Inspiratory Resistance as a Potential Treatment for Orthostatic Intolerance and Hemorrhagic Shock

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Convertino VA, Cooke WH, Lurie KG. ***Inspiratory resistance as a potential treatment for orthostatic intolerance and hemorrhagic shock.*** **Aviat Space Environ Med 2005; 76:319–25.**

Loss of consciousness due to central hypovolemia can occur due to sudden cardiovascular decompensation in normal individuals or hypovolemic shock in wounded patients. A variety of devices have been developed to sustain perfusion to the brain including anti-G suits worn by pilots and returning astronauts and applied to patients as “shock trousers.” However, all countermeasures developed to date suffer from problems that limit their utility in the field. An “impedance threshold device” (ITD) has recently been developed that acutely increases central blood volume by forcing the thoracic muscles to develop increased negative pressure, thus drawing venous blood from extrathoracic cavities into the heart and lungs. We review here a series of experiments that demonstrate the application of the ITD to a variety of experimental conditions, including its use to: 1) increase heart rate, stroke volume, and arterial BP in normovolemia and hypovolemia; 2) increase cerebral blood flow velocity; 3) reset cardiac baroreflex function to a higher operating range for BP; 4) lower intracranial pressure; and 5) reduce orthostatic symptoms. In this brief review, we present evidence which supports further consideration of using inspiratory resistance as a countermeasure against circulatory collapse associated with orthostatic instability and hemorrhagic shock.

Keywords: arterial pressure regulation, autonomic function, baroreflex, cardiac arrest, heat stroke, orthostatic hypotension.

MAINTENANCE of consciousness requires adequate perfusion to the brain, which may be compromised in a variety of physiological and clinical circumstances. Inability to tolerate upright standing posture due to development of severe orthostatic hypotension and syncope often plagues astronauts and military personnel in their austere operational environments. In the civilian sector, up to 30% of otherwise healthy young adults report at least one syncopal episode during their lifetimes, and syncope accounts for up to 3% of all emergency room visits in the United States (31). More critically, hemorrhagic shock remains a leading cause of death in both civilian and battlefield trauma (7). Syncope and hemorrhagic shock share the same underlying mechanisms, namely, central hypovolemia and cardiovascular decompensation. A countermeasure that functionally restores central blood volume would, therefore, be expected to prove useful for all of these conditions.

Battlefield injury often leads to hypovolemia through hemorrhage. In spaceflight, hypovolemia occurs as a response to microgravity over the first several days of exposure (15,30), persists regardless of flight duration, and contributes to postflight orthostatic intolerance and reduced exercise capacity (16,33). The usual countermeasures for all of these conditions include fluid replacement (resuscitation) and/or lower body counterpressure (shock trousers or G-suits). For spaceflight, these often fail to prevent symptoms of cardiovascular instability or even frank syncope on assuming an upright body position at 1 G (5). Tolerance for loss of central blood volume or orthostatic stress can be enhanced by means of centrifuge training (24) and maximal exercise bouts prior to orthostatic testing (23), but these procedures cannot be applied in spacecraft and remote settings or medical evacuation aircraft.

Low central blood volume contributes to a reduction in cardiac filling, stroke volume (SV), and arterial pressure (P_a). The resulting acute hypotension activates autonomically mediated compensatory mechanisms that evoke sympathetic nerve activity, tachycardia and peripheral vasoconstriction in an attempt to restore P_a (10). When the reduction in blood volume and P_a reach a critical level, activation of decompensatory mechanisms result in sympathetic withdrawal, bradycardia and vasodilation (10), a condition we refer to as circulatory collapse (11,19). Cardiovascular decompensation is the precursor to syncope or hemorrhagic shock. Therefore, any therapeutic approach that is designed to increase venous return and SV should counteract circulatory collapse. Increased negative intrathoracic pressure during spontaneous inspiration represents a natural mechanism for enhancing venous return and cardiac filling. Any device that applies resistance during inspiration takes advantage of this simple concept and shows promise as a mechanical facilitator of the respiratory pump that enhances venous return and preload

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This manuscript was received for review in August 2004. It was accepted for publication in January 2005.

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Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 APR 2005	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Inspiratory resistance as a potential treatment for orthostatic intolerance and hemorrhagic shock.	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Convertino V. A., Cooke W. H., Lurie K. G.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA FOrt Sam Houston, TX 78234	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a REPORT	b ABSTRACT	c THIS PAGE			
unclassified	**unclassified**	**unclassified**	**SAR**	**7**	

to the heart (35,38,44). In this review, we examine a series of experiments designed to evaluate the application of inspiratory resistance as a potential countermeasure to restore central blood volume and possibly improve clinical and critical outcomes.

Using the Chest as an Active Vacuum Pump

Cournand et al. (20) reported in an early study that venous return, ventricular preload, and subsequently cardiac output ($\dot{Q}$) decrease with positive pressure breathing sufficient to increase mean airway pressure. Guyton et al. (28) characterized the entire venous return curve in animals by plotting blood flow against pressures in the right atrium, and demonstrated marked increases in venous return when right atrial pressures were suctioned to −2 to −4 mmHg. Based on this simple concept of positive vs. negative intrathoracic pressures and their effects on venous return, it has been shown that increasing negative intrathoracic pressure through resistive breathing decreases left ventricular and right atrial pressures (38), consequently increasing left ventricular preload and SV index (39). The central hemodynamic response of resistive breathing is similar to that observed during Mueller maneuvers, where initial reductions of P_a due to reductions of left ventricular SV are followed by increases in P_a due to resulting increased venous return and consequent increases in left ventricular SV (25,41).

Negative intrathoracic pressure during the inspiration may be enhanced in several ways. In the experiments described here, a controlled level of inspiratory negative pressure was produced in humans by using an inspiratory threshold device (ITD) comprised of a plastic valve attached to a standard clinical facemask (36). Responses to ITD breathing were compared directly with a sham ITD device which provided zero inspiratory pressure (ZTD).

Central Hemodynamics

Changes of central hemodynamics in humans during resistive breathing were assessed in two human studies (13,14). During spontaneous breathing in the supine position, inspiratory impedance of approximately 6 cm H_2O increased heart rate (HR), P_a (13,14), SV (measured with thoracic bioimpedance) and $\dot{Q}$, and decreased total peripheral resistance (TPR) (14). Other countermeasures that restore central blood volume and protect SV and $\dot{Q}$ such as maximal exercise, G-suits, fluid loading, and centrifuge training may fall short of effective implementation due to practical limitations (6,23,24) or the inability to produce the immediate effects on central blood volume and hemodynamics similar to resistive breathing (24).

Autonomic Function

Although loss of blood volume contributes to postflight orthostatic intolerance in astronauts, reduction in the sensitivity of the carotid-cardiac baroreflex has also been implicated in hemodynamic instability following both simulated (17,21) and actual microgravity (26,27). Carotid-cardiac baroreflex function is restored in subjects after bed rest with application of maximal exercise 24 h prior to reambulation (23). Similarly, reductions of carotid-cardiac baroreflex sensitivity associated with reductions of central blood volume during lower body negative pressure (LBNP) are reversed with restoration of central volume during G-suit inflation (22). Stimulation of arterial and/or cardiopulmonary baroreceptors by oscillations in intrathoracic or arterial pressure (25) may acutely change the sensitivity of the carotid-cardiac baroreflex response (8,9) and affect autonomic compensation to orthostatic or hypovolemic challenges. The effects of inspiratory resistance on the carotid-cardiac baroreflex response were also tested in humans. During ITD breathing, cardiac baroreflex sensitivity was not altered but responses were shifted to higher arterial pressures (13). These results, together with prior work (14), support the hypothesis that negative intrathoracic pressure and baroreflex resetting induced by ITD breathing augments central hemodynamics and potentially increases the operational range of the baroreflex under conditions of severe hypotension.

Increased HR in conjunction with increased P_a could manifest through atrial stretch and activation of cardiopulmonary baroreceptors, but cardiopulmonary baroreflex activation and consequent interaction with arterial baroreceptors during inspiratory resistance can only be inferred and not measured directly in humans; it is likely that both cardiopulmonary and arterial baroreflexes operate to some degree and probably function at times in opposition (2). In addition, elevated HR and $\dot{Q}$ during spontaneous breathing on an ITD may simply reflect an "exercise" effect from the increased work of breathing against resistance. If this were true, one might expect withdrawal of vagal activity and no change or a slight increase in sympathetic activity with HR below 100 bpm (43). However, in experiments designed to test the mechanism(s) involved in the tachycardic response to inspiratory resistance, there was no change in ventilatory mechanics (volume and rate), metabolic rate, cardiac vagal activity as indicated by no effect on the percent of normal consecutive R-R intervals that vary by more than 50 ms (pNN50), and muscle sympathetic nerve activity (microneurography) (13). While that report involved only one subject, later work on an additional eight subjects confirmed that ITD breathing does not affect vagal-cardiac control as estimated from frequency domain analysis of R-R intervals, or directly measured peripheral sympathetic traffic (18). Those observations suggest that the elevation in HR is initiated by a mechanical rather than metabolic or primary autonomic stimulus, and therefore may not represent an "exercise" effect per se. Rather, a larger negative intrathoracic pressure resulting from inspiratory resistance may initiate mechanically a chronotropic response as a result of enhanced cardiac filling [e.g., the Bainbridge reflex, stretch of the SA node (1,2,42)].

Head-up tilt table experiments in astronauts prior to and immediately after the NASA Neurolab Space Mission (STS-90) revealed that increased muscle sympathetic nerve activity (MSNA) induced by moving from the supine to upright posture was associated with a reduction in SV (34). Although this finding was not unexpected, lower

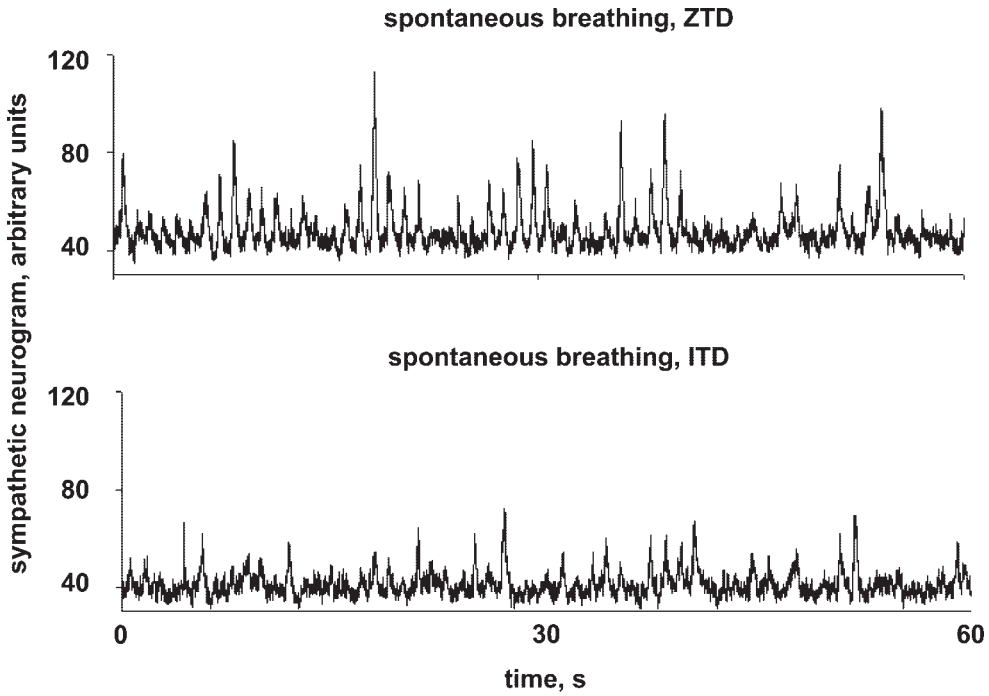

Fig. 1. Recording of neurograms from a subject during spontaneous breathing on a ZTD without inspiratory resistance (upper panel) and on an ITD (bottom panel). [From Convertino et al. (13).]

average SV and greater average MSNA measured after spaceflight in both supine and upright postures were positioned in a linear fashion on the same SV-MSNA stimulus-response relationship as the average preflight SV and MSNA responses (34). Using LBNP as a model for the investigation of mechanisms associated with hemorrhagic shock (19), we corroborated the linear relationship between SV and MSNA (10,11).

In addition to increasing cardiac filling (40) and SV (14), spontaneous inspiration on the ITD lowered TPR (14). Since higher SV and lower TPR are associated with lower MSNA in a linear fashion (10,11,34), it seemed possible that spontaneous breathing on an ITD would cause a reduction in MSNA. However, recent experiments show that resistive breathing had no effect on supine MSNA (15 ± 8 vs. 15 ± 9 bursts/min) despite significant increases in mean arterial pressure (MAP) (94 ± 7 to 99 ± 9 mmHg) in eight normovolemic, normotensive subjects (18). However, in one subject, a 23-ml (25%) increase in SV (measured with thoracic bioimpedance) during ITD breathing was associated with an MSNA of 23 bursts/min compared with 30 bursts/min when breathing on the ZTD (**Fig. 1**).

Those preliminary results support the hypothesis that large elevations in SV might produce proportionate reductions in MSNA. Morgan et al. (41) recorded MSNA responses within the respiratory cycle during prolonged (20-s) Mueller maneuvers and documented a biphasic response consisting of initial suppression of sympathetic traffic despite falling P_a followed by activation and resultant increases of P_a. The ITD study averaged MSNA over several minutes; biphasic responses could have contributed to the observation there of unchanged sympathetic traffic during resistive breathing. Since high sympathetic nerve activity is associated with poor clinical outcome in states of central hypovolemia (32), the ability of the ITD to reduce MSNA could be an effective countermeasure against syncope and hemorrhagic shock. Future experiments designed to induce more dramatic alterations in central hemodynamics, particularly in states of central hypovolemia, are necessary to test this hypothesis.

Cerebral Blood Flow

In a porcine model of cardiac arrest, cerebral blood flow (CBF) and neurological function were significantly protected by application of an ITD (35,37). Yannopoulos et al. (46) demonstrated in pigs that ITD breathing increases cerebral perfusion pressure (CPP), and increases CBF during cardiopulmonary resuscitation after cardiac arrest. **Fig. 2** shows a representative example of the changes in intrathoracic pressure measured in the trachea of the pig, and concurrent changes in intracranial pressure (ICP) measured in the brain parenchyma (Lurie KG, et al. Unpublished communication; 2004).

In this case, positive pressure ventilations were delivered every 8 s and after each breath. Use of an ITD in conjunction with positive pressure breathing generated an intrathoracic pressure of −10 mmHg and an immediate decrease in ICP by about 7.5 mmHg. The ITD also increased P_a (not shown). When the ITD was removed, ICP returned immediately to baseline levels. The impact of both ITD and positive pressure ventilation on ICP suggest a remarkable degree of concordance between changes in intrathoracic and intracranial pressures, which may have significant implications in the treatment of a number of disorders that alter CBF. These new findings also suggest that the vacuum created by the ITD causes a "waterfall" effect that increases blood flow by maximizing the pressure gradient across the cerebral circulation. Maintaining adequate CBF while reducing ICP could prove critical in

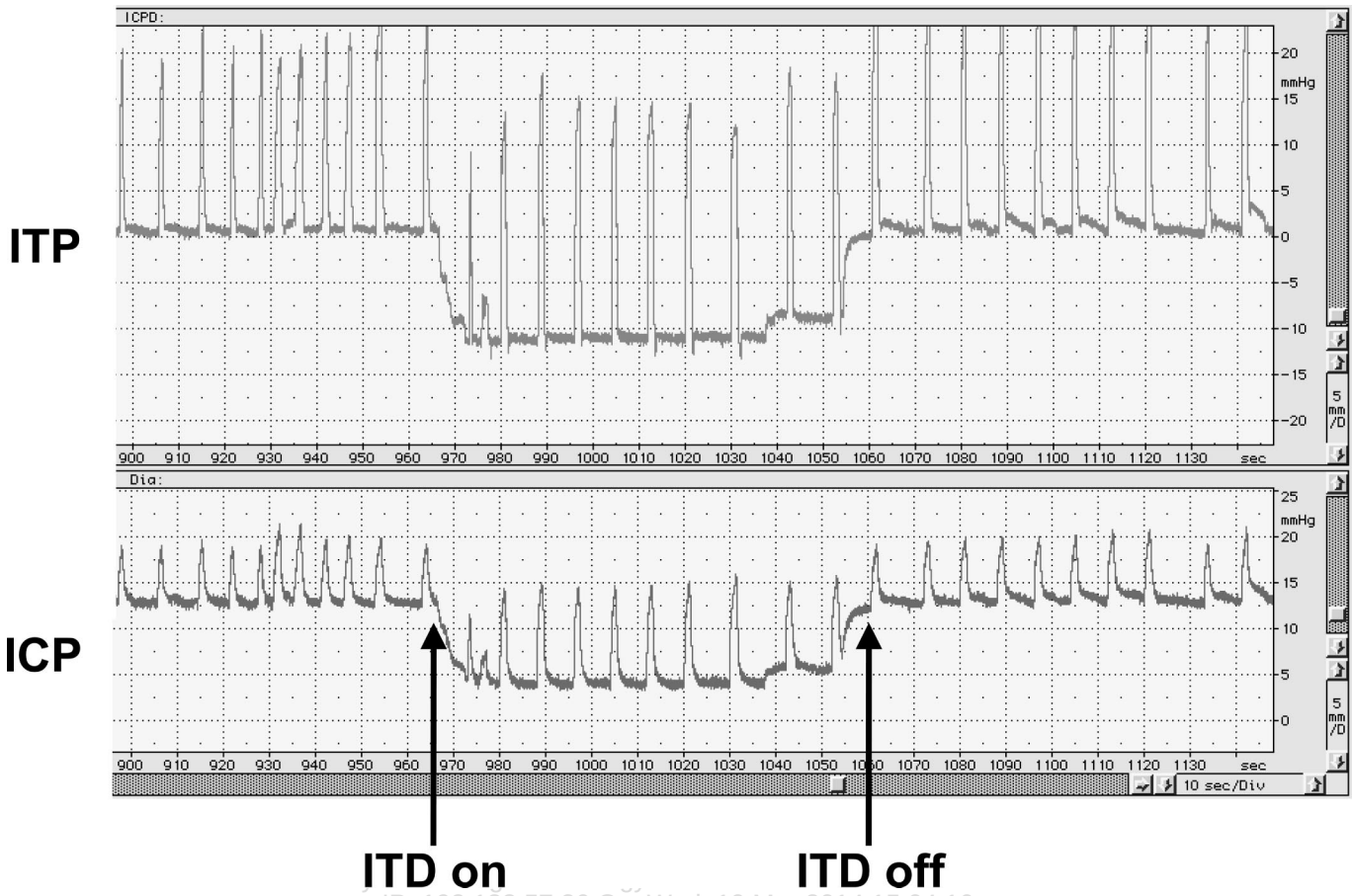

Fig. 2. Continuous recordings of intrathoracic pressure (ITP, upper tracing) and intracranial pressure (ICP, lower tracing) in an apneic pig in hemorrhagic shock before, during (ITD on), and at the cessation (ITD off) of application of an ITD modified for use in nonbreathing individuals. Positive pressure ventilations were delivered every 8 s when the ITD was applied. ITP was maintained at −10 mmHg in the absence of positive pressure ventilations.

prolonging or even preventing the progression to circulatory collapse associated with syncope and/or hemorrhagic shock.

Since inadequate cerebral perfusion ultimately leads to syncope and circulatory collapse (4), a device or procedure that effectively maintains or increases CBF might benefit returning astronauts or bleeding patients awaiting definitive medical care. Based on evidence from animal experiments (35,37,46) and the observation that subjects reported less severe symptoms (e.g., dizziness) during transition from the squat to standing posture (12), the effects of ITD breathing on CBF were investigated in humans. Cerebral blood flow velocity (CBFV) was recorded in the right middle cerebral artery in seven subjects using transcranial Doppler ultrasonography. **Fig. 3** shows a representative response recorded from one subject.

For all seven subjects, breathing through an ITD increased mean CBFV from 64 cm · s^{-1} during breathing on a ZTD to 69 cm · s^{-1} during ITD breathing ($p = 0.01$). End-tidal CO_2 for ITD breathing was 4.8 ± 0.1%, similar to that produced by the ZTD (4.9 ± 0.2%) (18). However, it is possible that increased respiratory drive during ITD breathing increased cerebral metabolic activity and therefore induced cerebral vessel dilation. The pulsatility index, an indirect estimate of cerebral vascular resistance tended to decrease with active ITD breathing ($p = 0.09$). The pulsatility index (calculated as the difference between peak systolic and end diastolic flow velocity divided by mean flow velocity) is clearly an imperfect estimate of cerebral vascular resistance that does not take into account systemic arterial, venous, or cerebro-spinal fluid pressures. However, in a prospective study of brain-injured

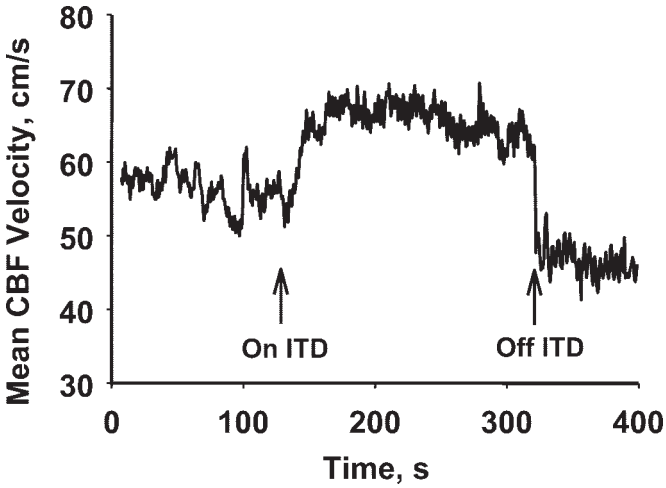

Fig. 3. Continuous recording of mean cerebral blood flow (CBF) velocity in a subject before, during (On ITD), and at the cessation (Off ITD) of spontaneous breathing on the ITD.

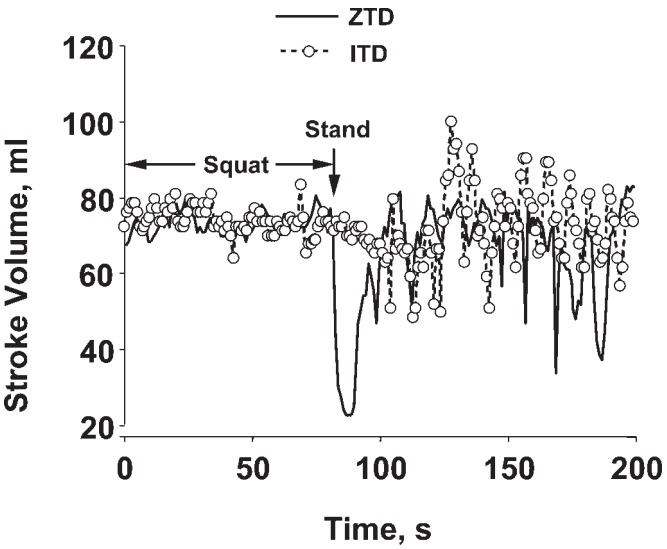

Fig. 4. Stroke volume responses in a subject undergoing the transition from a squat to a standing posture during spontaneous breathing on an ITD (open circle line) and ZTD (solid line).

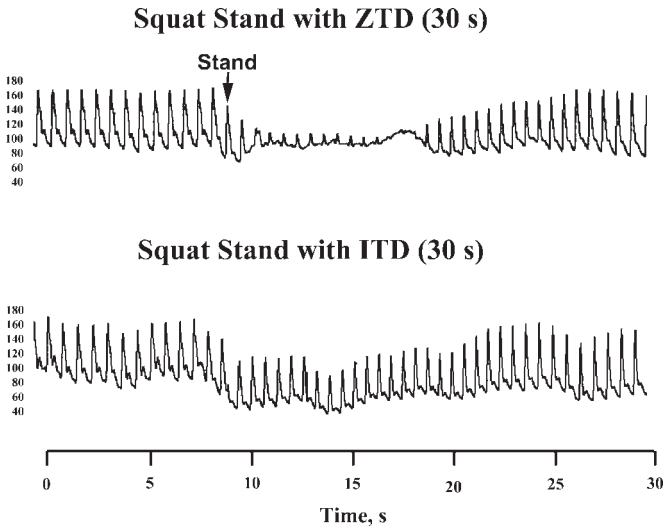

Fig. 5. Beat-to-beat arterial BP responses in a subject undergoing the transition from a squat to a standing posture during spontaneous breathing on a ZTD (upper panel) and on an active ITD (lower panel).

patients, Bellner et al. (3) found a strong correlation ($r = 0.94$; $p < 0.0001$) between ICP measured by intraventricular catheters and the pulsatility index; they concluded that the latter is a useful surrogate for ICP for monitoring severely brain injured patients (3). Because end-tidal CO_2 is an imperfect predictor of P_aCO_2, (45), and because even small changes in P_aCO_2 profoundly affect CBFV (29), it is possible that the observed increases in CBFV during ITD breathing resulted from increased cerebral metabolic activity and consequent dilation of the cerebral vasculature.

Orthostatic Stress

Resistive breathing might be expected to protect central hemodynamics against circulatory collapse induced by sudden orthostatic stress or hemorrhage (13,14). One study has addressed this possibility experimentally (12): 18 healthy, normotensive volunteers (9 males, 9 females), ages 20–56, completed two 6-min protocols in counterbalanced order with a ZTD or an ITD set to open at −7 cm H_2O pressure. An infrared finger photoplethysmograph was used to make noninvasive measurements of HR, SV, $\dot{Q}$, TPR, and MAP. Symptoms were recorded using a subject perceived rating (SPR) where 1 = normal and 5 = dizziness.

Movement from squat to stand reduced TPR by about 35% with or without the ITD, but the device affected other variables, as illustrated for one subject in **Fig. 4 and 5**. Using the ZTD, he experienced severe symptoms (SPR = 4) as his SV fell (Fig. 4), P_a was reduced and pulse pressure dropped to below 20 (Fig. 5). In contrast, the ITD prevented symptoms (SPR = 1), erased the acute, transient drop in SV (Fig. 4) and held pulse pressure at 60 mmHg (Fig. 5). The periodic increases in SV in Fig. 5 reflect the negative intrathoracic pressure induced by the ITD during inspiration.

On average for all subjects, MAP fell −36 ± 3 mmHg with the ZTD compared with −27 ± 4 mmHg with the ITD ($p = 0.03$) despite similar elevations in HR (15 ± 2 bpm, $p = 0.93$). SV changed by −8 ± 4% for ZTD vs. +2 ± 4% for ITD; the corresponding changes in $\dot{Q}$ were +10 ± 6% and +22 ± 5% ($p < 0.04$). The SPR was 1.4 ± 0.1 for ZTD vs. 2.0 ± 0.2 for ITD ($p = 0.04$). These results suggest that the ITD may defend against orthostatic hypotension and intolerance. Future experiments should address the effects of ITD breathing in subjects after a period of simulated microgravity or experimentally induced hypovolemia.

Simulated Central Blood Loss in Humans

The effects of inspiratory resistance were tested in human volunteers subjected to LBNP as a model for acute reduction of central blood volume due to hemorrhage (19). **Fig. 6** shows beat-to-beat SV measured with thoracic bioimpedance during baseline supine rest and

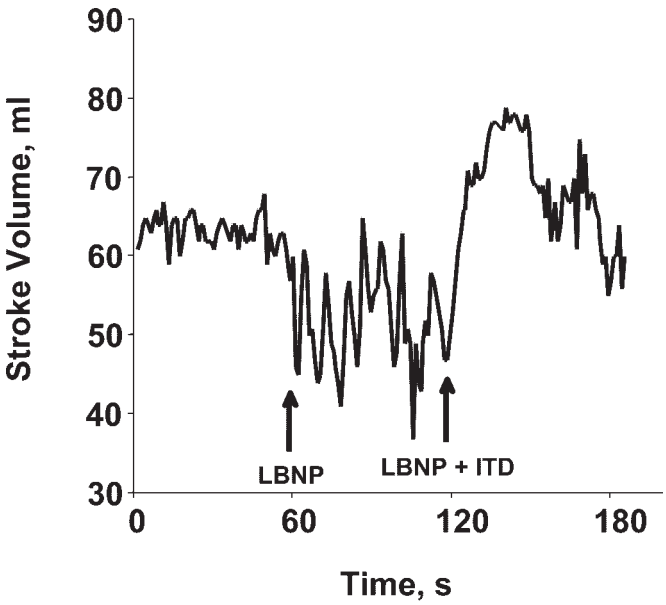

Fig. 6. Stroke volume responses in a subject undergoing simulated central blood loss by use of 60 mmHg LBNP during the transition from baseline rest to LBNP to LBNP and spontaneous breathing on an ITD.

exposure to 60 mmHg LBNP with normal breathing followed by use of an ITD (Convertino VA, et al. Unpublished communication; 2004).

In this case, the LBNP caused a 30–35% reduction in SV, while the ITD produced an immediate increase that overshot and then returned to baseline after 1 min. If such results are confirmed, the ITD might provide a critical bridge for maintaining P_a in the face of hemorrhage until volume replacement can be provided. Thus, the ITD may prove useful in civilian trauma and tactical combat care, especially for a bleeding patient with a weak or absent pulse.

SUMMARY

Countermeasures that increase central volume, restore or support adequate autonomic function, and increase or maintain cerebral perfusion should be effective in protecting against severe hypotension leading to syncope and/or hemorrhagic shock in astronauts and victims of severe trauma. Approaches developed through aerospace research such as fluid loading, use of G-suits, maximal exercise, and centrifuge training have been applied and have met with varying degrees of success. The primary limitation of such countermeasures is lack of practical utility in an operational setting. This review shows that inspiratory resistance may be an effective alternative to those methods and can be implemented using a device such as the ITD, which is small and lightweight enough to be carried in austere medical kits. Such a device could be used to reduce postflight orthostatic hypotension in astronauts, and to support brain perfusion in victims of severe traumatic blood loss.

ACKNOWLEDGMENTS

This research was supported by a Cooperative Research and Development Agreement between the U.S. Army Institute of Surgical Research and Advanced Circulatory Systems Inc. (CRDA No. DAMD17–02–0160), by funding from the U.S. Army Combat Casualty Care Research Program, and a Small Business Innovative Research grant funded by the U.S. Army Medical Research and Materiel Command (W81XWH-04-C-0022). The views expressed herein are the private views of the authors and are not to be construed as representing those of the Department of Defense or Department of the Army.

Disclaimer: K. Lurie is a co-inventor of the impedance threshold device and founded Advanced Circulatory Systems Inc. to develop the device.

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